

# Regulating the Fate of Pharmaceutical Drugs: A New Prescription for the Environment

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"Because this chemical is used as a pharmaceutical and in low quantities relative to other *chemicals*, it is not regulated by EPA."<sup>1</sup>

## I. INTRODUCTION

Increasing international attention has been given to the impact of pharmaceutical drugs on the environment. This attention primarily started with scientific studies in Europe, but the findings have since attracted the attention of scientists<sup>2</sup> and policymakers<sup>3</sup> in the United States. This interest has generated a growing body of literature that documents the presence of human and animal drugs, including hormones, antibiotics, and antineoplastic compounds,<sup>4</sup> in soil, lakes, rivers, and tap water. Although the detected levels are typically low, these compounds are biologically active compounds,<sup>5</sup> sometimes more active than their natural counterparts.<sup>6</sup> In fact, according to F.M. Christensen, a researcher at the Danish Toxicology Center, it is difficult for scientists to define levels below which there are no adverse effects.<sup>7</sup> The research also has shown that several of these chemicals are "environmentally persistent," stubborn chemicals that refuse to degrade readily.

There are several mechanisms that can be used in parallel or, in the alternative, to slow or reverse this trend. Three possible approaches are discussed in this paper. The first option is simply to do nothing: to let market forces work to achieve the optimal level of drug consumption given the newly defined awareness of the environmental consequences.

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<sup>1</sup> Taken from the NATIONAL TOXICOLOGY PROGRAM, REPORT ON CARCINOGENS, NINTH EDITION, "NORETHISTERONE" (Jan. 2001) [hereinafter NTP REPORT], available at <http://ehp.niehs.nih.gov/roc/toc9.html> (last visited Mar. 11, 1993). This statement was made in reference to the compound Norethisterone, a compound used in oral contraceptives that is, according to the report, "reasonably anticipated to be a human carcinogen." *Id.* In the United States Geological Survey study reported *infra*, this compound was found in U.S. waterways at higher concentrations than many industrially used synthetic organic chemicals and pesticides that were studied based on their widespread use.

<sup>2</sup> See Larry B. Barber, Herbert T. Buxton, Dana W. Kolpin, Edward T. Furlong, Michael T. Meyer, E. Michael Thurman & Steven D. Zaugg, *Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance*, 36 ENVIRONMEN. SCI. TECHNOL. 1202-11 (2002).

<sup>3</sup> Andrew C. Revkin, *F.D.A. Considers New Tests for Environmental Effects*, N.Y. TIMES, Mar. 14, 2000, available at <http://www.nytimes.com/2002/03/14/health/14POLL.html> (last visited Mar. 11, 2003).

<sup>4</sup> Antineoplastic compounds are those used to fight cancer cell growth.

<sup>5</sup> B. Halling-Sørensen & S.E. Jørgensen, *Drugs in the Environment*, 40 CHEMOSPHERE 691, 693 (2000).

<sup>6</sup> F.M. Christensen, *Pharmaceuticals in the Environment—A Human Risk?*, 28 REGULATORY TOXICOLOGY & PHARMACOLOGY 212, 217 (1998).

<sup>7</sup> *Id.*

The second, and perhaps most straightforward option, is to increase the capability of sewage treatment plants (STPs) to more effectively breakdown these compounds leaving only environmentally inert effluents.

A third option is to rely on the drug approval process of the Food and Drug Administration (FDA). Requiring a more rigorous assessment when applying for new drug approval would shift the focus to the root-cause of the problem. Unfortunately, the drug approval processes in the United States and in Europe historically have not required any real measure of these impacts. In the United States, since the passage of the National Environmental Policy Act (NEPA), FDA has been required to assess the environmental impact of all of its actions including the pre-approval marketing of drug compounds.<sup>8</sup> In January 1995, a similar assessment was demanded for drugs approved in the European Union.<sup>9</sup> While these measures may provide a starting point for effective analysis, neither of these provisions are focused on human beings as an endpoint impacted by the presence of these compounds in the environment.<sup>10</sup> The recent data that has been gathered indicates the problem is more complex than originally anticipated and emphasizes the need to reconsider the approach taken in performing an environmental assessment to assure compliance with the aims of NEPA.

It is possible, then, that FDA will respond to recent publications and bolster its requirements for manufacturer and internal agency assessments of the potential long-term impacts of market approval of new drugs. Improving the current regulatory system may be an adequate means of preventing further negative impacts on the environment. As more evidence of environmental impact accumulates, the argument for change within the agency becomes stronger.

In the event that FDA fails to act on the new information, it may be possible to seek judicial review of the agency's assessment through private-party challenges under the provisions of the Administrative Procedure Act (APA)<sup>11</sup> and NEPA. Despite a broad presumption of the reviewability of agency action, however, the court may resist substituting its judgment for that of the agency. This is because the availability of judicial review is limited by the Article III requirements and the scope of review is limited by the court's strong deference toward FDA in areas of the agency's expertise. On the other hand, newly available information may provide enough support for the argument that there has been a significant change in the underlying facts to warrant more active scrutiny of FDA's approach to environmental assessments.<sup>12</sup>

This article focuses substantial attention on the scientific realizations made over the last twenty years documenting the widespread contamination of the environment by human and animal drugs. The article then presents the risks that may be associated with the prevalence of these compounds in the environment. Combined, these provide a basis for the argument that changes are needed to alter the current course of pharmaceutical contamination of the environment. Three approaches to this problem are presented: a *laissez-faire* market solution, rethinking and redesigning sewage treatment, and relying on government regulation.

The discussion of regulation begins with an overview of FDA's current approach to environmental assessment and suggests changes that may be made in response to the new science that is unfolding. The final focus is on the availability of judicial review of FDA's action or inaction under the provisions of the APA. Issues of standing, ripeness, and the ultimate reviewability of the agency's action are discussed.

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<sup>8</sup> 43 U.S.C. § 4321 (2002).

<sup>9</sup> Christensen, *supra* note 6, at 212.

<sup>10</sup> *Id.*

<sup>11</sup> See generally 5 U.S.C. §§ 551-59, 701-06.

<sup>12</sup> See American Horse Protection Ass'n v. Lyng, 681 F. Supp. 949 (D.C. Cir. 1988).

## II. THE SYMPTOMS: THE SCIENTIFIC BACKGROUND

While scientists, interest groups, politicians, and eventually the chemical industry have focused attention on the environmental impact of industrial chemicals, little attention has been given to the fate of human drugs.<sup>13</sup> Based on the sheer magnitude of the bulk chemical industry, a macroscopic threat to the stability and health of the environment clearly became cognizable, even to the layperson, as rivers caught fire due to high levels of chemical contamination. Pharmaceuticals, on the other hand, are consumed in milligram quantities and their physical impact is relatively microscopic, making it difficult for the layperson to comprehend and technically difficult for scientists to detect. This impact appears to have been, for all intents and purposes, assumed to be *de minimis*.<sup>14</sup> Recent advances in analytical chemistry along with renewed attention have led to new scientific realizations that begin to invalidate many of the assumptions that provided the basis for a lack of attention.

### A. Early Indications of the Fate of Drugs

As early as 1981, researchers in the United Kingdom detected drugs in the aquatic environment at concentrations on the order of 1 µg/l.<sup>15</sup> More recently, advances in analytical tools have allowed detection of drug residues at concentrations in the low parts per trillion (ppt) range, which is 1000 times lower than had previously been detectable in a typical investigation. Equipped with these new techniques, researchers in Europe<sup>16</sup> and in the United States<sup>17</sup> have begun quantifying the buildup of drug compounds and their derivatives from the traces found in lakes, rivers, and groundwater supplies. These reports indicate the presence of low-level, but pervasive and persistent, anthropogenic<sup>18</sup> contamination of surface water and rivers.

#### 1. What Happens to a Drug Compound After Use?

The process of understanding the impact of therapeutic drug use starts with answering the question: "What happens after a drug has been used therapeutically?" The answer is fairly straightforward. A general model for the fate of human drugs is shown in Figure 1. Initially, a drug is consumed or injected to achieve the desired therapeutic result. But drugs are not always completely consumed during the therapeutic process and, often, a significant percentage of the drug actually leaves the body unchanged.<sup>19</sup>

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<sup>13</sup> Halling-Sørensen & Jørgensen, *supra* note 5, at 691.

<sup>14</sup> The prevailing view has been that the low levels of consumption and excretion will have little or no impact and thus the potential problems created have been dismissed as trivial.

<sup>15</sup> Thomas A. Ternes, *Occurrence of Drugs in German Sewage Treatment Plants and Rivers*, 32 WATER RES. 3245, 3245 (1998).

<sup>16</sup> See generally Hans-Rudolf Buser, Markus D. Müller & Thomas Poiger, *Occurrence and Environmental Behavior of the Chiral Pharmaceutical Drug Ibuprofen in Surface Waters and in Wastewater*, 33 ENVIRONMEN. SCI. TECHNOL. 2529-35 (1999); Ternes, *supra* note 14; Wolfram Baumann, Silvana Vianna Rodrigues, Marcus Stumpf, Thomas Ternes & Rolf-Dieter Wilken, *Polar Drug Residues in Sewage and Natural Waters in the State of Rio de Janeiro, Brazil*, 225 THE SCI. OF THE TOTAL ENVIRONMENT 135-41 (1999).

<sup>17</sup> See Barber et al., *supra* note 2.

<sup>18</sup> Anthropogenic contamination is contamination that is the result of human activity and development.

<sup>19</sup> Klaus Haberer, Roman Hirsch, Karl-Ludwig Kratz & Thomas Ternes, *Occurrence of Antibiotics in the Aquatic Environment*, 225 THE SCI. OF THE TOTAL ENVIRON. 109, 110, Table 1: Human Prescription Amounts and Excretion Rates of Antibiotics, column on excretion percentage unchanged (1999).

The residual active compounds, along with any metabolites resulting from the body's breakdown of the drug, leave the body in excreted urine or feces and make their way to the local STP.

The possible fate of pharmaceutical drugs following sewage treatment can be summarized as follows:<sup>20</sup>

- (1) the drug and/or its metabolites may be broken down into carbon dioxide and water;
- (2) the drug and/or its metabolites are persistent throughout the treatment process and depending on the chemical properties of the drug,<sup>21</sup> some amount of the compound may remain in the sludge, which will be a solid discharge from the STP; and
- (3) the drug and/or its metabolites are persistent but do not bind to the solids and are discharged with the treated sewage effluent.

When focusing on specific drugs, the removal efficiency of the treatment step is as low as seven percent and never provides complete elimination.<sup>22</sup> This means that significant amounts entering treatment leave unchanged in either the plant effluent or the solid sludge discharged from the plant. Treatment plant effluent eventually mixes with groundwater, which is the primary source of the U.S. drinking water supply. The solid waste generated during sewage treatment is either spread on the surface of fields in agriculture or is landfilled. The runoff from the fields, along with any leachate that escapes from the landfills, eventually merges with groundwater, potentially reaching the drinking water supply.

Veterinary drugs reach the same end but follow a more direct path. Poultry and cattle are treated with hormones and antibiotics that are eventually excreted in manure and urine. These enter the groundwater as runoff and are not susceptible to treatment.<sup>23</sup> Fisheries, which have become increasingly drug-intensive, often involve direct application to source water.

## 2. *Better Tests Provide New Results*

Although this may seem like a tortuous path for what appears to be a negligible amount of medicine, current studies report that significant amounts of these compounds are making their way through this system and into the environment. A study published in 1983 indicated the presence of a series of antibiotics and other compounds in samples taken from river water.<sup>24</sup> In 1984 and 1985, scientists reported the detection of hormones in river and drinking water samples.<sup>25</sup> Further studies followed reporting the detection of antineoplastic agents in hospital wastewater effluents.<sup>26</sup>

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<sup>20</sup> Halling-Sørensen & Jørgensen, *supra* note 5, at 691-93.

<sup>21</sup> The tendency to bind with the sludge will depend on several different properties of each compound being treated and will vary based on pH and other factors that may influence the affinity of the compound to bind with the solid sludge. *Id.* at 693.

<sup>22</sup> Ternes, *supra* note 14, at 3247, Figure 1: Elimination of Different Drugs During Passage Through a Municipal Sewage Treatment Plant.

<sup>23</sup> F. Ingerslev, S.E. Jørgensen, H.C. Holten Lützhøft, S. Nors Nielsen & B. Halling-Sørensen, *Occurrence, Fate and Effects of Pharmaceutical Substances in the Environment—A Review*, 36 CHEMOSPHERE 357, 372 (1998) (anticipating antibiotics used will have a fate analogous to pesticides).

<sup>24</sup> *Id.* at 365.

<sup>25</sup> *Id.* (citing G.W. Aherne, J. English & V. Marks, *The Role of Immunoassay in the Analysis of Microcontaminants in River Samples*, 9 ECOTOXICOLOGY & ENVIRON. SAFETY 79-83 (1985)).

<sup>26</sup> *Id.* at 365 (citing T. Steger-Hartmann, K. Kümmerer & J. Schecker, *Trace Analysis of the Antineoplastic Ifosfamide and Cyclophosphamide in Sewage Water by Two-Step Solid Phase Extraction and Gas Chromatography-Mass Spectrometry*, 84 J. OF CHROMATOGRAPHY A 179 (1996)).

### 3. *The Problem With Fish Farms and Antibiotic Accumulation*

After the initial reports found drugs and hormones in the environment, scientists began focusing on the link between drug use patterns and the contamination detected. Studies of the sediment of fish farms give a basic illustration. These studies have shown that the use of antibiotics in fish farming leads to the contamination of the local sediment.<sup>27</sup> They report concentrations of oxytetracycline, an antibiotic, as high as 4.9 mg/kg dry matter.<sup>28</sup> The data also indicate that the antibiotics commonly used are relatively persistent and do not break down in the environment. Oxytetracycline was found to have an estimated half-life of approximately ten weeks,<sup>29</sup> meaning that after the sediment has been contaminated once, it will take ten weeks for the concentration to fall to half the initial contamination levels. Thus, with repeated exposure, even over relatively long time cycles, the contamination will accumulate.

### 4. *Sewage Treatment of Excreted Human Drugs Offers Little Improvement*

As compared to the fish antibiotics released directly into the environment, commonly used human drugs will be treated in a local STP before reaching the environment. Although this may seem like a significant improvement over direct application in the environment, field research confirms that current treatment methods are inadequate. A 1998 study comparing samples taken before and after treatment through a German STP shows that drugs, representative of those found in a typical medicine cabinet, can be found in both the feed and the discharge of the facility. Researchers found detectable amounts of drugs ranging from over-the-counter anti-inflammatory compounds to prescription lipid regulating agents.<sup>30</sup> The polar lipid regulating agents bezafibrate and gemfibrozil were especially ubiquitous and were detected in a majority of the STP effluents studied. Despite the eighty-three percent efficient removal of bezafibrate, the compound was found in the treatment discharges at concentrations up to 4.6 µg/l with a median value of 2.2 µg/l.<sup>31</sup> Although the unpolar lipid regulators (i.e., clofibrate, etofibrate, and fenofibrate) were not generally detected in the STP effluents, presumably due in part to the affinity to bind with the treatment sludge, concentrations of their polar metabolites were measured in excess of 1 µg/l.<sup>32</sup> These compounds provide a powerful example of the need to understand the complex biochemistry behind drug metabolism and molecular transformations. Without a thorough understanding, environmental assessments may be looking at the wrong form of the drug, or for an altogether different compound.

Occurrence of detectable levels of analgesics and anti-inflammatory drugs also is widespread.<sup>33</sup> Compounds such as diclofenac, ibuprofen, indometacine, naproxen, ketoprofen, and phenazone all have been detected in treatment plant effluent with the majority of detected concentrations for some of the compounds lingering above 1 µg/l.<sup>34</sup> The widespread occurrence of these compounds intuitively appears to be the result of their extensive use and nonprescription availability.

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<sup>27</sup> *Id.* at 365.

<sup>28</sup> *Id.* (citing L. Berglind & P. Jacobsen, *Persistence of Oxytetracycline in Sediments From Fish Farms*, 70 *AQUACULTURE* 365-70 (1988)).

<sup>29</sup> *Id.*

<sup>30</sup> Ternes, *supra* note 14, at 3247.

<sup>31</sup> *Id.* at 3251.

<sup>32</sup> *Id.*

<sup>33</sup> *Id.*

<sup>34</sup> *Id.*

In addition to these more common medications, some of the more rarely prescribed pharmaceuticals, including psychiatric drugs and various cancer treating agents, also have been found in quantifiable concentrations in STP effluents and in the aquatic environment.<sup>35</sup> Compounds such as ifosfamide and cyclophosphamide, both antineoplastics, and carbamazepine, an anti-epileptic drug, have been found at detectable levels.<sup>36</sup> Although typically the occurrence of drugs such as the antineoplastics may be tied to high-level discharges from local hospitals treated by the facility, effluent from a rural treatment plant that is not tied to a specific point-source also showed elevated levels of ifosfamide, reaching as high as 2.9 µg/l.<sup>37</sup>

The German study found carbamazepine at detectable levels in over half of the treatment plants tested.<sup>38</sup> This widespread occurrence of carbamazepine was coupled with relatively high concentrations. For the STP effluents studied, the high concentration was 6.3 µg/l and the ninetieth percentile concentration was 3.7 µg/l.<sup>39</sup> A similar trend was seen when testing for the compound in rivers,<sup>40</sup> indicating what may be the strong chemical persistence of the compound. This illustrates that although many drugs are not subject to widespread use, other factors such as the relative inefficiency of treatment and persistence in the environment may lead to detectable occurrence and, thus, potential negative impacts.

### 5. *Corroborating Data From the Rio Study*

A study undertaken in Rio de Janeiro, Brazil, which focused on thirteen compounds (eleven drugs and two metabolites) shows a remarkably similar pattern of contamination. Although the concentrations detected in Brazil were lower than levels found in other research, the trends match almost perfectly.<sup>41</sup> For those compounds investigated in both studies, the range of removal rates through treatment also was similar.<sup>42</sup> Detectable concentrations of many of the drugs also were found in the Paraíba do Sul—the river Rio de Janeiro primarily relies on as its source of drinking water.<sup>43</sup> The mirroring trends shows that these results may be generalizable to some degree.

### 6. *The U.S. Geological Survey Fills in the Domestic Picture*

Scientists from the U.S. Geological Survey (USGS) recently performed a comprehensive study of contamination in the United States. The study investigated the low-level contamination of streams by pharmaceuticals, hormones, and other organic chemicals.<sup>44</sup> The study focused on ninety-five organic compounds, several of which are used as antibiotics, steroids, hormones, and other prescription and nonprescription drugs.<sup>45</sup>

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<sup>35</sup> The research indicates finding the psychiatric drug diazepam as well as two chemotherapy drugs, ifosfamide and cyclophosphamide, in German STP discharges. Carbamazepine, an antiepileptic drug, also made its way in detectable concentrations to rivers. *Id.*

<sup>36</sup> *Id.* at 3252.

<sup>37</sup> *Id.* at 3251.

<sup>38</sup> *Id.* at 3250, Table 6: Concentrations of Diazepam, Carbamazepine and Anticancer Agents in STP Effluents as Well as Rivers and Streams.

<sup>39</sup> *Id.*

<sup>40</sup> *Id.*

<sup>41</sup> Baumann, *supra* note 15, at 138. Based on a comparison between the compounds presented in the two papers.

<sup>42</sup> *Id.*

<sup>43</sup> *Id.* at 139.

<sup>44</sup> Barber et al., *supra* note 2, at 1202-11.

<sup>45</sup> *Id.* at 1203.

The study indicates that pharmaceutical drugs account for some of the most pervasive organic wastewater contaminants on the same order of magnitude as compounds receiving significantly more attention.<sup>46</sup> Acetaminophen, the active ingredient in Tylenol, was detected in nearly twenty-five percent of the streams sampled with a maximum concentration of 10 µg/l.<sup>47</sup> Cotinine, a nicotine metabolite, was found in over thirty percent of the streams surveyed with concentrations approaching 1 µg/l.<sup>48</sup>

Prescription drugs and antibiotics were found less often, with the average frequency of detection per-compound typically in the range of –zero to ten percent and with the highest frequencies in the –ten to fifteen percent range.<sup>49</sup> Of the prescription drugs studied, codeine and gemfibrozil, a lipid regulator, were detected at the highest levels at 1.0 and 0.79 µg/l respectively.

Antibiotics show a wide frequency distribution in U.S. streams, ranging from nondetectable levels to just under thirty-seven percent occurrence. The highest concentration of antibiotics detected was around 2 µg/l, though the compounds with the highest detected levels were not necessarily those most frequently detected.<sup>50</sup> This illustrates the multifaceted nature of this problem.

Steroids and hormones also were detected with significant frequency.<sup>51</sup> Although some of the hormones detected are naturally occurring, the report indicates significant concentrations of synthetic hormones, which are used as ovulation inhibitors in oral contraceptives.<sup>52</sup> These synthetic hormones frequently are more potent hormones than their natural counterparts, and many are listed carcinogens.<sup>53</sup> Norethisterone, a hormone used in oral contraceptives, was found at higher levels than all other hormones, both natural and unnatural, and at higher levels than many of the other compounds studied.<sup>54</sup> This compound is listed in the National Toxicology Program's report as "reasonably anticipated to be a human carcinogen."<sup>55</sup>

### 7. *The Ultimate Fate: Drinking Water*

In addition to environmental samples, prescription drugs are showing up in drinking water samples as well. Researchers in Berlin found low levels of clofibrilic acid, a metabolite of a human lipid regulator, in at least one drinking water sample taken from each of the districts of Berlin.<sup>56</sup> Research in the United States indicated that the average concentration of estrone reached 35 ppt in tap water at Tulane.<sup>57</sup>

#### B. *Limitations on the Scientific Data*

There are several limitations that impede a full assessment of the true extent of the problem. Before the impact of the use of a drug can be assessed, scientists need a fairly

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<sup>46</sup> *Id.* at 1207, Figure 2: Measured Concentrations for the 30 Most Frequently Detected Organic Wastewater Contaminants.

<sup>47</sup> *Id.*

<sup>48</sup> *Id.*

<sup>49</sup> *Id.*

<sup>50</sup> *Id.*

<sup>51</sup> *Id.*

<sup>52</sup> *Id.*

<sup>53</sup> See NTP REPORT, *supra* note 1.

<sup>54</sup> Barber et al., *supra* note 2, at 1202-11, Table 1: Summary of Analytical Results of Streams Sampled for 95 Organic Wastewater Contaminants.

<sup>55</sup> NTP REPORT, *supra* note 1.

<sup>56</sup> Ingerslev et al., *supra* note 22, at 365.

<sup>57</sup> J. Raloff, *Excreted Drugs: Something Looks Fishy*, 157 SCIENCE NEWS 388 (2000), available at <http://www.sciencenews.org/20000617/fob1.asp> (last visited Mar. 13, 2003).

complete model of the drug-human interaction. Scientists operating without a clear metabolic picture may be looking for the wrong compound in the wrong place, or they may not be focusing on the most persistent or the most toxic form of the compound.<sup>58</sup> In both of these scenarios, research fails to provide an accurate measure of the problem. Scientists also are technically limited by a lack of reference standards and appropriate detection methods. This prevents quantitative analysis and thorough investigation into compounds that are otherwise of interest because of their prevalent use or potential toxicity.<sup>59</sup>

Uncertainties in the drug's biological interactions are further compounded by the possibility of chemical changes that may take place after excretion. Chemical reactions in excreted wastes and even reactions in the sewage treatment process<sup>60</sup> can lead to reversion of metabolized drug derivatives back into their original active counterparts. This means that drugs can be metabolized into inactive compounds—at which point they may be thought not to pose a significant problem—and then subsequently can revert back to the active compound once in the environment. Estimating the impact of a given drug compound simply from data on drug use and patient metabolic information then becomes inadequate. It also may explain why scientists occasionally find that the concentration of a compound actually increases after discharge from STP and further dilution in the environment.<sup>61</sup>

Variations in chemical persistence, which may lead to enhanced long-term concentrations through bioaccumulation, also increases the problems associated with making firm estimations of the fate, concentration, and potential impact of these compounds. And although field-based sampling may give the most accurate picture, these results may be confounded by contributions from industrial discharges.<sup>62</sup>

### III. SO WHAT? TRANSLATING THESE OBSERVATIONS INTO POTENTIAL EFFECTS

Research indicating the presence of these compounds without an attempt to understand the potential effects does nothing to further public interest in this issue. The logical question is, "So what?" Indeed, some researchers make the claim that the human risk from current drug consumption patterns is "negligible."<sup>63</sup> This conclusion, however, presents an extremely shortsighted view, and appears to ignore the impact on micro-organisms and aquatic life that may, when completely played out, lead to deleterious effects for humans. One must keep in mind that these compounds are designed and exploited for their biological activity, even at extremely low concentrations<sup>64</sup> and, as an environmental issue, there are several intermediates in the cycle between human use and the potential for eventual human exposure. Each of these intermediates, from microscopic plant life to fish, may be impacted by exposure throughout the cycle. These impacts may have both direct and indirect effects on human health, as well as on the human environment, and should not be ignored when making a determination of human risk.

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<sup>58</sup> See Ternes, *supra* note 14, at 3251. The research done did not detect widespread occurrence of non-polar lipid regulators, but the polar metabolites were found in significant concentrations.

<sup>59</sup> See *id.* at 3252; Barber et al., *supra* note 2, at 1205.

<sup>60</sup> Ternes, *supra* note 14, at 3252.

<sup>61</sup> *Id.* at 3249-50, Tables 3-6 (a comparison between the concentration of the studied compounds in the rivers and streams with the STP effluents shows that there are occasionally significant increases in concentration going from the concentrated STP discharge to the diluted rivers).

<sup>62</sup> *Id.* at 3251.

<sup>63</sup> Christensen, *supra* note 6, at 219.

<sup>64</sup> Ingerslev et al., *supra* note 22, at 357.



Hormone-regulating drugs can take effect at concentrations as low as a few nanograms per liter, which is a level that is 1000 times less concentrated than the 1 µg/l range at which many of these compounds have been found.<sup>65</sup> For example, estradiol, the female sex hormone and a pollutant found in U.S. streams,<sup>66</sup> has been demonstrated to alter the sex characteristics of certain fish at concentrations as low as twenty parts per trillion (ppt).<sup>67</sup> The levels detected in the rivers were up to ten times this concentration.<sup>68</sup> At even lower concentrations, 0.1 ppt ethynylestradiol (a hormone used in oral contraceptives) and 10 ppt estrone; some male fish exhibit both male and female reproductive tissues.<sup>69</sup> At higher levels, 1 ppb, of either of these compounds, these hormones transform all males into females.<sup>70</sup> Levels detected in U.S. streams approach this level.<sup>71</sup>

Measurable effects are not limited to these laboratory predictions. Several researchers have found intersex fish in U.S. waters including the Great Lakes.<sup>72</sup> These fish exhibit both male and female sexual characteristics and do not naturally reproduce.<sup>73</sup> In addition, the fish often show further biological signs of sexual dysfunction.<sup>74</sup> The location of these sexually ambiguous populations of fish has been connected to the proximity to the influx of discharge from STPs.<sup>75</sup>

The presence of these sexually altering hormones is not limited to discharges from sewage treatment facilities. The previously noted survey of Tulane's tap water showed that this contamination appears to have come full circle, finding average estrone concentration of 35 ppt and concentrations as high as 80 ppt.<sup>76</sup> While the effect of these concentrations on humans is not clear, it is known that these hormonally active compounds can work synergistically with other natural and synthetic chemicals, thus increasing the potential threat and confounding the independent evaluation of their impact.<sup>77</sup>

Antibiotics present a unique situation in that they represent a kink in the truism that the poison is proportionate to the dose. While it is true that the intended effects of antibiotic use are proportionate to the dosage, other serious effects such as bacterial resistance are a greater threat at lower doses.<sup>78</sup> This inverse relationship makes resistance a credible threat even at low concentrations, and may be a serious threat to public health—posing the potential for an increase in the number of infections that are untreatable with available antibiotics.<sup>79</sup> Antibiotic resistant bacteria have been discovered in sediment bacteria exposed to oxolinic acid, an antibiotic used in fish farming.<sup>80</sup> Bacterial resistance also is widespread in U.S. rivers.<sup>81</sup> Though the results are sporadic,

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<sup>65</sup> *Id.*

<sup>66</sup> Barber et al., *supra* note 2, at 1202-11, Table 1: Summary of Analytical Results of Streams Sampled for 95 Organic Wastewater Contaminants.

<sup>67</sup> Janet Raloff, *Drugged Waters*, 32 *SCIENCE NEWS* 187-89 (1998).

<sup>68</sup> Barber et al., *supra* note 2, at 1202-11, Table 1: Summary of Analytical Results of Streams Sampled for 95 Organic Wastewater Contaminants.

<sup>69</sup> Raloff, *supra* note 56.

<sup>70</sup> *Id.*

<sup>71</sup> Barber et al., *supra* note 2, at 1204-05, Table 1: Summary of Analytical Results of Streams Sampled for 95 Organic Wastewater Contaminants.

<sup>72</sup> Raloff, *supra* note 56.

<sup>73</sup> *Id.*

<sup>74</sup> *See id.*

<sup>75</sup> *See id.*

<sup>76</sup> *See id.*

<sup>77</sup> *See* Barber et al., *supra* note 2, at 1210.

<sup>78</sup> Haberer et al., *supra* note 18, at 112.

<sup>79</sup> *Id.*

<sup>80</sup> Ingerslev et al., *supra* note 22, at 373-80, Table 4: Toxic Effects of Medical Compounds on the Environment).

<sup>81</sup> J. Raloff, *Waterways Carry Antibiotic Resistance*, *SCIENCE NEWS*, June 5, 1999, at 356, available at [http://www.sciencenews.org/sn\\_arc99/6\\_5\\_99/fob1.htm](http://www.sciencenews.org/sn_arc99/6_5_99/fob1.htm) (last visited Mar. 13, 2003).

there are several indications of bacterial resistance to ampicillin, a penicillin family antibiotic, as well as to tetracycline.<sup>82</sup> Exposure to contaminated water is blamed for the antibiotic resistance found in Canadian geese whose exposure to antibiotics is solely through the environment.<sup>83</sup> This macroscopic manifestation of the potential for the microbial changes has scientists pointing the finger toward the heavy use of antibiotics and asking for more restrained use.<sup>84</sup>

Another effect, which may be a more cognizable threat to human health, is genotoxicity.<sup>85</sup> Genotoxic activity has been strongly correlated to the causation of cancer. In one survey, wastewater from hospitals exhibited genotoxic activity in thirteen percent of the samples.<sup>86</sup>

Several things can be learned from the lengthy presentation of scientific research into the fate and effects of drug compounds in the environment. First, the data is extremely limited, which makes it difficult to generate a comprehensive scientific picture. While new analytical techniques are providing some insight, it is not likely that independent research alone will provide a sufficient assessment of the problem because of an incomplete understanding of several of the interactions drugs have within the body and beyond. Pharmaceutical science has done an amazing job discovering compounds used to affect measurable results in clinical use but has done little to investigate beyond the immediate gratification of an efficacious clinical trial. Proper assessment of the problem requires the good faith of pharmaceutical manufacturers as well as a concerted effort by regulatory agencies to provide scientific support and in-house evaluations. The current limitations on the data make the assessment of the existing contamination lead to the conclusion that the current evaluation is the only best-case scenario and that with proper policing, additional realities lay waiting to be uncovered.

Second, the analysis of the effects is equally unclear because the science is fraught with limitations. The relevance of laboratory findings to concrete environmental impacts can be quickly questioned and discarded and the lack of toxicological data on many of the compounds found in the environment makes the burden of demonstrating potential effects even more unrealistic.

While the findings in both of these areas overwhelmingly indicate the need for further information, they also lead to concrete realizations that attempt to sum up the problem.

- Human and animal drugs are present in the environment at levels above 1 ppb. This may be attributed to the combination of widespread use, the inefficiency of treatment systems to remove these compounds, and their general persistence in the environment.
- Many of these compounds have the ability to harm both the human environment and, ultimately, human beings. Findings in nature corroborate laboratory results showing quantifiable effects such as antibiotic resistance and hormonal dysfunction.
- Although there is new information, the development and use of drugs has far outpaced any assessment of the impact beyond the therapeutic use. Gaps in information on the metabolism, bioconversion and degradation, and ultimate fate of

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<sup>82</sup> See *id.*

<sup>83</sup> See *id.*

<sup>84</sup> See *id.*

<sup>85</sup> A genotoxin is defined as "a toxin (poisonous substance), which harms the body by damaging DNA molecules, causing mutations, tumors, or neoplasms." The genotoxicity is a measure of this ability to harm the DNA and potentially cause mutations, tumors and neoplasms. THE LIFE SCIENCE DICTIONARY, at <http://biotech.icmb.utexas.edu/search/dict-search.phtml?title=genotoxin> (last visited Mar. 13, 2003).

<sup>86</sup> Ingerslev et al., *supra* note 22, at 383.

drugs as well as the potential effects need to be addressed to fully assess current and future drug approvals.

#### IV. TOWARD A NEW PRESCRIPTION FOR DRUG APPROVAL AND USE

##### A. *Nonregulatory Approaches to Address Pervasive Drug Contamination in the Environment*

Pharmaceutical use is a personal and vital part of modern life. One of the primary arguments against making changes to agency regulation in this arena is that the benefits of the use of these drugs vastly outweigh the significance of these findings. Any additional restriction on drug availability would result in direct detrimental impacts on the health and well being of modern society. Admittedly, the benefits of many of these drugs hardly can be debated but the increasing amount of scientific research may indicate a need for a more cautious approach to drug regulation and use. There are several ways to address this problem.

###### 1. *The “Do Nothing” Approach*

One approach would be to allow market forces to drive to an optimal level of drug use and an acceptable level of subsequent impact—basically a “do nothing” approach that relies on consumer education to drive to more sustainable pharmaceutical drug-use patterns.

This *laissez-faire* approach has at least two limitations. First, accounting for the scientific concerns requires an extremely high level of sophistication on the part of the consumer. It would seem to be a safe assumption that even at a relatively high level of sophistication, an accurate accounting for these concerns is unlikely. There also is the problem of collective action. Each person’s contribution to concentrations found in the environment is discrete and is negligible on its own. With each consumer acting in the best interest of his or her own immediate health, it seems unrealistic to think that consumers will shift demand in proportion to impacts that research has identified. Without the appropriate incentives, no single consumer can grasp the costs and benefits of his or her own individual contribution in a way that leads to a substantial change in personal health habits.

###### 2. *Improve and Adapt Universal Sewage Treatment*

A second, more active, approach is to address the inadequacy of current sewage treatment methods—an approach that also has several drawbacks. First and foremost, it fails to correct the root-cause of the problem, i.e., drugs that are used for both human health and animal development are finding their way into the environment and are accumulating at significant levels. Fundamentally, this has to do with the design and the use of the drugs themselves. Addressing the problem downstream of the source may not provide the right incentives to lead to a long-term or cost-effective solution.

Second, this solution is under-inclusive. It does not address the large amounts of animal drugs that make their way directly into the environment. While independent contributions of various drug uses are often hard to distinguish, the research clearly indicates that proper assessment of this problem cannot ignore the impact of compounds that are not subject to formal treatment and reach the environment directly.

Technically, there also is a question of feasibility. While the idea of building idealized treatment plants with universally high removal rates is attractive, it may not be scientifically workable. The flexibility required to deal with the range of compounds fed into the system would make operational design a remarkable, if not impossible, challenge. Even if such a system were feasible, across-the-board removal of these compounds likely would make it prohibitively expensive to build and operate.

The follow-up question that then must be addressed is, "Who pays for such a system?" One option is to force the cost of these improvements on the current municipal treatment providers. This works if the costs are minimal, but, due to technical complexities, this is unrealistic. There could be a fee paid by the drug manufacturer to, in some way, account for the total impact of the volume of drugs it sells. Or, on the other hand, a fee could be charged to the consumer, similar to a tax on the purchase of drugs. The problem is that both of these translate to an increase in the cost of medicine making these options unpopular with the consumers and insurers who would be responsible for shouldering the burden of the increased costs.

In addition, increasing the responsibilities of the waste treatment provider raises complicated issues of compliance. Presumably, operation of these facilities would require additional permits and approvals. There would need to be an initial regulatory validation of the efficiency of the system to verify the performance of the facility as well as a mechanism of ongoing monitoring for compliance with discharge standards. These facilities would need to be flexible enough to respond to efficiency changes due to natural events, increased loading due to changes in market use, and the changing chemistries due to variations in compounds in the feed when new drugs are phased in and out of widespread use.

### *3. Moving Toward Government Regulation*

Overall, these "downstream" methods may provide some protections, but are limited and lack the ability to address the fundamental problem. FDA, the initial interface with drug manufacturers before marketing and consumer use, however, is situated to deal with this problem at its root: drug design and use. Regulation at the front-end can provide incentives for manufacturers to move toward more comprehensive drug design, optimizing a proposed formulation for safety and effectiveness as well as for its impact on the environment. Regulation also may lead to a more thorough investigation of the biological chemistry of a compound beyond the desired therapeutic effects and, ideally, to a more complete understanding of the fate and effects of both the used and excreted drug compounds.

#### *B. Overview of the Current Regulatory Approach to Environmental Assessment*

Under the Federal Food, Drug, and Cosmetic Act, FDA has the responsibility for ensuring that human and animal drugs are both safe and effective.<sup>87</sup> This responsibility was expanded into the environmental realm by enactment of the National Environmental Policy Act (NEPA), which not only provides FDA with the authority to bring environmental considerations into its decisionmaking, but also requires that it take these considerations into account.<sup>88</sup> The purpose of the NEPA is to make environmental consid-

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<sup>87</sup> 21 U.S.C.A. § 355 (2002).

<sup>88</sup> See 42 U.S.C.S. §§ 4321 et seq.

erations a part of agency decisionmaking proceedings as early as possible, requiring agencies to produce an account of the long-term impact of the action considered as well as any environmental consequences initially not addressed.<sup>89</sup> The specific responsibilities and procedures required by FDA are codified in 21 C.F.R. § 25.

FDA's drug approval process is long and complex. NEPA planning begins when a drug manufacturer submits an Environmental Assessment in conjunction with its application for drug approval or when FDA consults with the applicant on the NEPA-related aspects of the approval.<sup>90</sup> Either an Environmental Assessment or a claim of categorical exclusion<sup>91</sup> is required with all applications requesting FDA action pursuant to 21 C.F.R. § 25.15. The assessment must address the relevant environmental issues, containing enough information for the agency to determine whether the proposed drug approval may "significantly affect the quality of the human environment."<sup>92</sup> The agency then evaluates the assessment for accuracy and objectivity and determines whether to require further analysis with the preparation of an Environmental Impact Statement.<sup>93</sup> If it is determined that there may be significant impacts,<sup>94</sup> FDA prepares an Environmental Impact Statement, which further investigates the environmental issues surrounding the agency's proposed action and addresses any potential alternatives.<sup>95</sup> If the findings in the Environmental Assessment do not warrant further investigation, the agency issues a Finding of No Significant Impact (FONSI).<sup>96</sup>

### 1. *Categorical Exclusion from Environmental Assessment*

The environmental assessment for most FDA actions, unless it meets the requirements for a categorical exclusion, begins and ends with the submission of an Environmental Assessment. FDA significantly reduced the requirement for the submission of an Environmental Assessment by broadening the class of categorical exclusions to include situations in which the "estimated concentration of the substance [the drug under consideration by the agency] at the point of entry into the aquatic environment will be below 1 part per billion."<sup>97</sup> This exception, which relies on extremely limited predictive estimates, creates a loophole for many of the low-level compounds discharged into the environment. The amendments also include exceptions applicable to naturally occurring drugs,<sup>98</sup> including potentially dangerous hormones. Ironically, these compounds are of primary concern to scientists because of their biological activity at low levels.

FDA regulations governing animal drugs contain a similar set of exceptions for categorical exclusions.<sup>99</sup> These exceptions include a broad exception for agency action on a new drug application (NDA) for a drug intended for nonfood animal use.<sup>100</sup>

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<sup>89</sup> *Boston v. Volpe*, 462 F.2d 254 (Mass. App. Ct. 1972).

<sup>90</sup> 21 C.F.R. § 21.10 (2002).

<sup>91</sup> Categorical exclusions are defined in 21 C.F.R. § 25.31, which lists the agency actions deemed not to have a significant impact on the environment.

<sup>92</sup> 21 C.F.R. § 25.15(a).

<sup>93</sup> *Id.* § 25.15(b).

<sup>94</sup> *Id.* § 25.22. This section states that there are no classes of FDA actions that routinely require the agency to prepare an EIS.

<sup>95</sup> *Id.* § 25.42.

<sup>96</sup> *Id.* § 25.15(b).

<sup>97</sup> *Id.* § 25.31(b).

<sup>98</sup> *Id.* § 25.31(c).

<sup>99</sup> *Id.* § 25.33.

<sup>100</sup> *Id.* § 25.33(d)(1).

## 2. *An Exception to the Exclusions*

These exceptions, most importantly those made for concentrations expected to be below 1 part per billion, appear to limit the responsibility of the agency and the drug sponsor significantly. There is, however, an exception to these exceptions. Section 25.21 provides that "FDA will require at least an Environmental Assessment for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment."<sup>101</sup> An example of such circumstance is an action where the available data "establish that, at the expected level of exposure, there is potential for serious harm to the environment."<sup>102</sup> It can be argued by the agency, and, if necessary, by those challenging agency action, that data for many active drug compounds suggest that there is such a potential for significantly "affecting the quality of the human environment" even at levels below 1 ppb. This re-opens the possibility of requiring an Environmental Assessment by the drug manufacturer even when only low levels are expected.

Despite the series of mechanisms that the FDA uses to quantify the environmental impact of its actions, the agency has never rejected an NDA on the basis of an environmental assessment.<sup>103</sup> There is some indication, however, that the release of new data may change the hands-off approach. In response to the recent publication of the USGS study on drugs in U.S. streams there was some indication by FDA that it may need to re-evaluate its position in light of new developments.<sup>104</sup>

## C. *Strengthening the Current FDA Framework for Environmental Review*

As noted, FDA has the authority to take a more active role in the protection of the environment within the framework of its current environmental assessment. Compelled by the new scientific findings, FDA could strengthen the environmental review within the current framework to more effectively address these new concerns. First, the agency could enhance the scrutiny of the agency's review of the initial Environmental Assessment submitted by the drug sponsor. Rather than relying on outmoded assumptions about the fate and effects of pharmaceutical compounds, FDA could use data from the recent studies as a basis for predicting environmental impact based on compounds with analogous drug chemistry and market use. This review would target those classes of compounds that have already manifested effects on the environment, such as hormones and antibiotics.

A more stringent FDA assessment would lead to the generation of toxicological data and analytical techniques previously not necessary for approval. The combination of better scientific understanding by the agency, and a more comprehensive background assessment by the manufacturer, would increase the frequency of more thorough Environmental Impact Assessments.

In addition to bolstering the environmental review prior to drug approval, FDA should provide a means of ongoing review of the actual environmental effects of drug compounds. This may be best achieved through collaboration with the Environmental Protection Agency and other government agencies. Another possibility is to provide an

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<sup>101</sup> *Id.* § 25.21.

<sup>102</sup> *Id.* § 25.21(a).

<sup>103</sup> Ingerslev et al., *supra* note 22, at 384.

<sup>104</sup> Andrew C. Revkin, *F.D.A. Considers New Tests for Environmental Effects*, N.Y. TIMES, Mar. 14, 2002, available at <http://www.nytimes.com/2002/03/14/health/14POLL.html> (last visited Mar. 13, 2003).

internal means through which a third-party can challenge an existing approval with the submission of scientific data on the studied environmental impact, which would then initiate a formal re-assessment within FDA.

Although incorporating changes similar to those suggested to respond to the data can modify the current FDA review, the agency's reaction to date appears to be to downplay the results of the USGS investigation's findings. This may be an indication that a more adversarial solution is required to compel the agency to respond.

## V. JUDICIAL REVIEW TO COMPEL AGENCY ACTION

The lengthy background on recent scientific discoveries in this area is included to support the contention that something must be done systematically in order for FDA to comply with the policies of NEPA. The growing body of information partially presented above, while admittedly lacking in scope and firm conclusions, indicates a significant shift in background facts and assumptions that should be driving agency policies and practice. These discoveries should be compelling FDA, through the mandate Congressionally dictated by NEPA, to demand a more thorough assessment of the use of each drug approved for marketing.

If the data does not, on its own, drive some change with regard to the emphasis on Environmental Assessments and Environmental Impact Statements by FDA, particularly with regard to drug manufacturers, interested groups may be able to petition the courts for judicial review of the agency's failure to respond.

### A. *The Citizen Petition and the Availability of Judicial Review*

Agency action, such as the approval for marketing of a new drug, is presumed to be subject to judicial review.<sup>105</sup> This is limited by the exhaustion requirement—that the party seeking review of agency action must “exhaust” their administrative remedies prior to obtaining judicial review in court.<sup>106</sup>

The Administrative Procedure Act (APA) provides that federal agencies must provide a means for interested parties to petition for the repeal, modification, or creation of rules.<sup>107</sup> FDA formally provides a “citizen petition” as a mechanism for petitioning to modify existing or creating new regulations.<sup>108</sup> Under the requirements for exhaustion of agency remedies, this provision becomes a prerequisite to legal action.<sup>109</sup> The citizen petition effectively allows the agency to consider the action within the agency and to exercise their expertise in deciding whether, and if so, how, to address it before the court is allowed to interfere.

The agency is not required to take action on the petition within a fixed time period, although the agency must give some indication of the status of the petition within 180 days of its filing.<sup>110</sup> When the agency has finally addressed the petition, the response, whether action or inaction, is presumed to be final agency action subject to judicial review.

### B. *Judicial Review Under the APA*

The APA further limits the availability of judicial review by precluding review in two cases: 1) when the governing statute precludes review<sup>111</sup> and 2) when the action is

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<sup>105</sup> 5 U.S.C. § 551-706.

<sup>106</sup> See *Myers v. Bethlehem Shipbuilding Corp.*, 303 U.S. 41 (1938).

<sup>107</sup> 5 U.S.C.A. § 553(e).

<sup>108</sup> 21 C.F.R. § 10.30.

<sup>109</sup> *Id.* § 10.45.

<sup>110</sup> *Id.* § 10.30(e)(2).

<sup>111</sup> 5 U.S.C. § 701(a)(1).

committed to agency discretion by law.<sup>112</sup> The first question, whether judicial review is explicitly excluded by statute, becomes one of statutory construction. Ultimately the reviewing court looks for Congressional intent to prohibit judicial review. This limitation has been interpreted by the Supreme Court as narrowed to "those rare instances where 'statutes are drawn in such broad terms that in a given case there is no law to apply.'"<sup>113</sup> The Court further defined the "no law to apply" limit as one in which a reviewing court would have no "meaningful standard" against which to measure the agency's action.<sup>114</sup>

Section 505(h) of the FDCA may be viewed as an implicit preclusion of review to nonapplicants. By outlining the means of appeal for an applicant of a new drug,<sup>115</sup> the argument can be made that the right to appeal should be construed as limited to the applicant, precluding a similar right of appeal by an interested third party. This argument, however, is not supported by the Court's requirement that the statute provide "clear and convincing" evidence of Congress's intention to restrict access to judicial review.<sup>116</sup> The failure by Congress to recognize a means for third parties to challenge FDA action does not express the clear intent to extinguish the presumption of review granted by the APA.

The second limit to judicial review deals more with the substance of the petitioner's claim,<sup>117</sup> the nature of the action that is being challenged. In this case, it is important to note that there are two potential claims that can be brought. The first claim is addressed at those drugs that already have been approved and seeks revocation or modification to the existing drug approval. This claim may be construed as a challenge to FDA's *inaction* in the failure to re-address previously approved drugs. The second, and more obvious, claim is one brought to challenge the approval of an NDA, which is plainly a challenge to agency *action*. The availability of judicial review and the amount of deference a court will reserve to the agency may be dependent on how the claim is framed.

In either the case of action or inaction, the "governing substantive statute"<sup>118</sup> is the NEPA mandate that FDA "insure that presently unquantified environmental amenities and values may be given appropriate consideration in decisionmaking along with economic and technical considerations."<sup>119</sup> This provision of NEPA requires that environmental considerations be made in addition to the traditional scope of FDA's inquiry when approving a drug. When a petitioner is seeking review of the agency's failure to appropriately consider the significance of recent developments in data on the fate of drugs in the environment, the law to apply is clear: there is a Congressional mandate that such data be part of the record on which action is based. The claim crystallizes into an allegation that the agency has not taken all of the congressionally-mandated factors into account and has therefore acted arbitrarily.<sup>120</sup>

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<sup>112</sup> *Id.*

<sup>113</sup> *Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402 (1971).

<sup>114</sup> *Heckler v. Chaney*, 470 U.S. 821 (1985).

<sup>115</sup> "An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside." 21 U.S.C.A. § 355(h).

<sup>116</sup> See *Abbott Laboratories v. Gardner*, 387 U.S. 136, 141 (1967).

<sup>117</sup> Cass R. Sunstein, *Reviewing Agency Inaction after Heckler v. Chaney*, 52 U. CHI. L. REV. 653, 658 (1985).

<sup>118</sup> *Id.*

<sup>119</sup> 42 U.S.C. § 4332(b).

<sup>120</sup> See *Citizens to Preserve Overton Park*, 401 U.S. at 402.



A similar analysis exists when the challenge is made to the agency's failure to revoke approval. The primary difference is that the data did not exist or was not available for consideration with the original application for drug approval. The charge then looks similar to the claim made in *American Horse Protection Association v. Lyng*.<sup>121</sup> The decision in *Lyng*, which forced the agency to issue new rules, was driven by the petitioner's challenge that newly published scientific data represented a significant change in the underlying facts that had provided the basis for the agency's initial rulemaking.<sup>122</sup> The challenge in this case follows a similar argument: that a significant change in the background facts regarding the environmental impact of a drug requires that the agency reconsider the regulation of the drug based on the whole record including the newly available information.

The policy behind deference to the agency, that based on their expertise the agency is better equipped than the court is to make the required judgment, also is weakened in this instance because of the nature of the law that is being applied and the realm of FDA's expertise. The law requires assessment of those actions that significantly affect the human environment<sup>123</sup>—an inquiry requiring application of a standard that is not squarely within the expertise of FDA, unlike decisions traditionally left to agency discretion.<sup>124</sup>

### 1. *Standing—Finding the Proper Plaintiff to Challenge Agency Action Injury in Fact*

Finding the right plaintiff to meet the standing requirements under section 702 of the APA and under Article III may be the biggest challenge to obtaining judicial review of FDA action in this case.<sup>125</sup> Article III requires three things as a constitutional minimum for standing: 1) injury in fact, 2) there must be a causal connection between the injury and the conduct complained of, and 3) it must be "likely" that it will be "redressed by a favorable decision."<sup>126</sup> In addition to these constitutional limits, the Court also applied prudential limits to plaintiff standing.

The injury in this case is defined by NEPA as "harm to the human environment." In *Lujan*, the Supreme Court said that a so-called "generalized grievance" based on an injury common to the public as a whole was impermissible,<sup>127</sup> which may limit a claim based on environmental impacts felt by the general public. The Court has since retreated from this position, narrowing this restriction to cases where the injury is "not only widely shared, but is also of an abstract and indefinite nature."<sup>128</sup> The Court went on to say that the fact that the injury is widely shared does not disqualify Article III standing and that where the harm is "concrete" the Court may find sufficient injury in fact.<sup>129</sup> This narrowing reduces the limitation on generalized grievances to a prudential consideration of the Court that is subject to the discretion of the Court rather than a constitutional limit on standing that cannot be ignored by the Court nor explicitly overridden by Congress. Although widely shared, the accumulating data makes it clear that this is indeed a concrete injury that is not suffered purely in the abstract.

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<sup>121</sup> See *American Horse Protection Ass'n v. Lyng*, 681 F. Supp. 953 (D.C. Cir. 1988).

<sup>122</sup> *Id.* at 953-58.

<sup>123</sup> See generally 21 C.F.R. § 25.

<sup>124</sup> See *Heckler v. Chaney*, 470 U.S. 821 (1985).

<sup>125</sup> See *Lujan v. Defenders of Wildlife*, 504 U.S. 555 (1992).

<sup>126</sup> *Id.* at 560 (citing *Simon v. Eastern Kentucky Welfare Rights Org.*, 426 U.S. 26, 41-42 (1976)).

<sup>127</sup> *Id.* at 575.

<sup>128</sup> *FEC v. Akins*, 524 U.S. 11, 23 (1998).

<sup>129</sup> *Id.* at 23-24.

In addition to addressing the concrete nature of the injury, the plaintiff may benefit from distinguishing his or her injury from that of the general public based on a specific nexus to the impact on the environment. This may be necessary to meet the standing requirements expressed in *Friends of the Earth*.<sup>130</sup> Justice Ginsberg, speaking for the Court, clarified that in environmental cases it is not "injury to the environment but injury to the plaintiff" that is necessary for meeting Article III standing.<sup>131</sup> This requirement in essence decreased the requirement for standing and allowed the Court to adjudicate the claim despite the fact there was no scientific proof of injury to the environment.<sup>132</sup> The Court re-iterated the discussion from *Sierra Club v. Morton*<sup>133</sup> and *Lujan* that a particular concern for the environment impacted as well as an ongoing connection to an affected area does adequately allege injury in fact.<sup>134</sup> It would appear then, that if the plaintiff can be distinguished by stating an environmental nexus and pleading distinct concern for the environment by making the claim that members of the organization are directly impacted through their ongoing and immediate connection to the impacted environment, this might be adequate injury for judicial review.

## 2. Fairly Traceable and Redressable?

The second requirement, that a causal connection between the injury and the action complained of exists, appears straightforward. These drugs generally would not be in widespread use without FDA approval and regulation. The challenge may be made, however, that FDA will reach the same conclusion on how to regulate a given drug, even after full consideration of the most recent scientific findings.

This defense was raised by the FEC in *Akins*.<sup>135</sup> The Court acknowledged that an agency has discretion about "whether or not to take a particular action,"<sup>136</sup> but went on to distinguish judicial review from complete deference to this discretion stating that "those adversely affected by a discretionary agency decision generally have standing to complain that the agency based its decision upon an improper legal ground."<sup>137</sup> The Court admitted that the same decision might be reached on lawful grounds, but found this did not indicate a failure to meet the requirements for an injury that is both "fairly traceable" as well as "redressable."<sup>138</sup>

## 3. The NEPA "Zone of Interest"

An additional requirement for standing under NEPA is that the party challenging the agency action is within the "zone of interest" protected by the act.<sup>139</sup> The zone of interest protected by NEPA has been interpreted to include detrimental effects on water quality.<sup>140</sup> NEPA itself indicates that the protection of water quality is an important policy provided for in the statutory scheme.<sup>141</sup> The congressional intent behind the

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<sup>130</sup> See *Friends of the Earth, Inc. v. Laidlaw Environmental Services (TOC), Inc.*, 528 U.S. 167 (2000).

<sup>131</sup> *Id.* at 181.

<sup>132</sup> *Id.* at 194-95.

<sup>133</sup> *Sierra Club v. Morton*, 405 U.S. 727 (1972).

<sup>134</sup> *Friends of the Earth*, 528 U.S. at 183.

<sup>135</sup> *FEC v. Akins*, 524 U.S. at 25.

<sup>136</sup> *Id.*

<sup>137</sup> *Id.* (citing *Abbott Laboratories v. Gardner*, 387 U.S. 136, 140 (1967); *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 410 (1971)).

<sup>138</sup> *Id.*

<sup>139</sup> *Stuabe v. Shalala*, 895 F. Supp. 1178, 1188 (W.D. Wis. 1995).

<sup>140</sup> *Sabine River Authority v. U.S. Department of the Interior*, 951 F.2d 669, 675 (5th Cir. 1995).

<sup>141</sup> See 42 U.S.C. §§ 4321, 4332(c).

passage of NEPA indicates that the “zone of interest” created by the act sufficiently includes those allegedly injured due to the degradation in water quality as can be claimed in this case.

#### 4. *Scope of Review*

The success of the suggested challenged depends first on getting the claim into court, and second on convincing the court that there are significant enough interests to warrant judicial intrusion into the agency’s decisionmaking process. Success depends on how the court defines the scope of its review. Typically, a reviewing court’s inquiry into agency action is limited to whether the agency decision was arbitrary and capricious.<sup>142</sup> This review is conducted on the whole administrative record and is deferential to the agency’s expertise and discretion.<sup>143</sup> Judicial review under the arbitrary and capricious standard is meant to determine whether the agency in taking action “has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.”<sup>144</sup>

Although the court’s standard of review is deferential, it does not blind the court from probing into changes in the underlying facts or into the agency’s failure to consider relevant information at the time of their decisionmaking.<sup>145</sup> This is in accord with the Supreme Court’s assessment of NEPA that it “merely prohibits uninformed—rather than unwise—agency action.”<sup>146</sup>

Based on this newly published scientific data, a challenge can be made that the agency’s decision is in fact uninformed. The agency mechanism in place to determine “significant environmental impacts” and weigh a given action against possible alternatives, which is procedurally housed in FDA’s current NEPA assessment scheme of 21 C.F.R. § 25, has failed to generate the information required for the agency to make an “informed” assessment of existence and magnitude of the relevant environmental impact. Ironically, it is the availability of third-party data, and not data submitted by the drug sponsors nor data generated by FDA in performing an Environmental Impact Study, that is bringing to light the true impact (to the best of its scientific ability) of the agency’s action on the environment. This information is not only scientifically relevant to FDA’s decision on the approval of a drug, but also is a legally necessary component of any good-faith effort to “protect and enhance the quality of the environment.”<sup>147</sup> Certainly, this information cannot be ignored once it is known.

In addition, this information, which calls into question many of the assumptions that underlie FDA’s historical approach to environmental assessments, should be interpreted as a signal that more data needs to be generated and addressed before a drug is approved. In a sense, the “radical change in its factual premises”<sup>148</sup> creates a new

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<sup>142</sup> *Overton Park*, 401 U.S. at 413.

<sup>143</sup> See *Motor Vehicle Mfrs. Ass’n v. State Farm Mutual Auto Ins. Co.*, 463 U.S. 29, 43, 77 (1973).

<sup>144</sup> *Maier v. United States EPA*, 114 F.3d 1032, 1044 (10th Cir. 1997) (citing *Motor Vehicle Mfrs. Ass’n v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. at 29, 43).

<sup>145</sup> See *American Horse Protection Association v. Lyng*, 681 F. Supp. at 953-58; *Maier*, 114 F.3d at 1040.

<sup>146</sup> *Robertson v. Methow Valley Citizens Council*, 109 S. Ct. 1835, 1846 (1989) (quoting *Kleppe v. Sierra Club*, 427 U.S. 390, 410 n.21 (1976)).

<sup>147</sup> Executive Order No. 11,514 of Mar. 5, 1970, 35 Fed. Reg. 4247, as amended by Executive Order No. 11,991 of May 24, 1977, 42 Fed. Reg. 26,967.

<sup>148</sup> *American Horse Protection Association v. Lyng*, 812 F.2d 1, 5 (D.C. Cir. 1987).

standard of relevance that requires a broader investigation beyond the bounds of the agency's previous assumptions. Anything less would be entirely failing "to consider an important aspect of the problem," thus making it both arbitrary and capricious.

If the reviewing court is convinced that the new information is relevant and that it significantly changes the factual grounds for the agency's action, the reviewing court can then force FDA to take action.<sup>149</sup> This applies to FDA's action of approving new drugs as well as potentially to their "inaction," or the agency's refusal to institute procedures to re-evaluate or revoke existing approvals. Although court interference with an agency's refusal to act is rare,<sup>150</sup> it is recognized that an obligation to act can be imposed by the court in cases where there have been significant enough changes in the legal or factual circumstances to require the issue to be re-addressed.<sup>151</sup>

It is worth pointing out that judicial review may be most warranted in the case of agency inaction on a prior-approved drug that FDA refuses to revoke or revisit. Only in this case will there be specific data on the actual impact of that compound on and in the environment. Any pre-approval assessment, even when it is done in light of the new data, will be based purely on severely limited predictive estimates. The scientific case may then be much stronger in the case of drugs that have been approved and are in widespread use, and samples can be taken making the fate of the drug known rather than predicted. On the other hand, estimates of environmental impact used for new approvals should be made in light of data for analogous drugs in current use, and error should be on the side of caution, because the risks of widespread use may be irreversible.

### 5. *The Goal of Judicial Intrusion*

At this point, it is important to clarify the goal of judicial review in this instance. Judicial review, both the case of action or inaction, is aimed solely at insuring that the agency has considered all of the relevant information necessary to make an informed, scientific decision that balances the interests of the agency, consumer drug users, and the policies of NEPA. There is little, if any, guarantee that for a given drug the agency will change its decision. The important goal, however, is that the FDA review mechanism requires the generation and consideration of data that has been made relevant by the recent findings. The court cannot be asked to tell an agency what decision it will make, but rather it is asked to make sure that the decision made is lawful and is based on full consideration of all relevant factors. In light of these considerations, judicial review will provide an incentive to drug manufacturers, and to the agency, to develop scientific standards and improve the scientific methods that currently limit the availability and accuracy of the scientific data presented.

The hope is that with an adequately informed FDA sitting as gatekeeper to this highly profitable market, drug design will evolve. This will lead drug companies to internalize the external impacts of their products and, where feasible, design drugs of the future that are noted for their minimal impact on the environment as well as for their therapeutic effectiveness. With this new pressure, drug designers may realize new ways to improve the bioavailability of a given compound and may make increased efforts to optimize drug therapy in a way that minimizes waste. The new data provides a stark criticism of current drug use and design, but with the proper incentives in place the data can be constructive in leading to a more sustainable concept of therapeutic drugs.

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<sup>149</sup> See *American Horse Protection Association v. Lyng*, 681 F. Supp. at 953-58; *Maier*, 114 F.3d at 1040.

<sup>150</sup> *WWHT, Inc. v. FCC*, 656 F.2d 807, 818 (D.C. Cir. 1981).

<sup>151</sup> *Bechtel v. FCC*, 294 U.S. App. D.C. 124 (D.C. Cir. 1992).

## VI. CONCLUSION

The data generated over the last twenty years documenting the occurrence and potential effects of human and animal drugs in our environment indicates the need for a significant shift in the way the environmental impact of pharmaceutical drug use should be viewed. FDA cannot remain willfully blind to these findings and continue to rely on outmoded assumptions and inadequate predictions to comply with the federal mandate to assess and weigh environmental impact under NEPA. It is an arbitrary and capricious abdication of its duty under the federal scheme, if the agency fails, in light of new evidence, to consider all of the relevant indicators of the environmental impact of its actions. Proper consideration based on existing and newly generated data calls for a new approach to drug approval and design. Although there are possible alternatives to agency regulation, FDA is best situated to target the root cause and create workable incentives to develop technology to design and regulate drugs that minimizes the impact on human health and the environment. While it is likely that a long-term solution will require improvements in waste treatment as well as shifts in consumption patterns, it is clear that FDA should take a leading role in acknowledging the problem and should issue a new prescription that more adequately addresses the growing environmental problems.

Figure 1



